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Gravidity, parity, blood pressure, and mortality among women in Bangladesh from the HEALS cohort

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Abstract

Background: Hypertension is an established risk factor affecting morbidity and mortality for a variety of cardiovascular diseases. Despite a hypothesized connection of reproductive history with hypertension and mortality, the nature of this association is poorly characterized. We evaluated the association of parity and gravidity with blood pressure, hypertension, and all-cause mortality.

Methods: 21 634 Bangladeshi women from the Health Effects of Arsenic Longitudinal Study (HEALS) cohort were included in this analysis. Linear and logistic regression models estimated the relationship between parity and gravidity with blood pressure and hypertension, respectively. Cox proportional hazards models estimated the relationship with all-cause mortality only among women aged > 45 years.

Results: Diastolic blood pressure was lowest in women with parity one (reference) and elevated in nulliparous women (adjusted % change = 3.12; 95% CI: 1.93, 4.33) and women with parity ≥ 2 (adjusted % change = 1.71; 95% CI: 1.12, 2.31). These associations were stronger for women aged > 45 years. Similar association patterns were observed in relation to hypertension. Further, in nulliparous women aged > 45 years, 265 deaths (6.6%) were ascertained during the follow-up period (median follow-up time = 8 years) and we observed suggestive elevated risks of all-cause mortality (adjusted HR = 3.83; 95% CI: 0.74, 19.78). The relationships between reproductive history, blood pressure, hypertension, and mortality were similar when modeling reproductive history as gravidity rather than parity.

Conclusions: For women in rural Bangladesh, nulliparity and nulligravidity appear to be associated with higher blood pressure and subsequent elevated risks of mortality.

Key words: Public health, epidemiology, hypertension

Strength and limitations of this Study

- This is a large prospective cohort study in a developing country context.
- Childbearing history was self-reported and menopause status was not ascertained.
- Unmeasured confounders may remain unaccounted for in our analyses.

INTRODUCTION

Elevated blood pressure is an established risk factor for cardiovascular diseases (CVDs) [1, 2], and complications of hypertension account for approximately 9.4 million deaths worldwide [3]. In Bangladesh, as in other South Asian countries, hypertension is a significant health concern with an overall prevalence of 26.4% among adults, with a higher prevalence (32.4%) in women [4].

A woman's risk for developing hypertension is influenced by several factors including age, body mass index (BMI), menopause, dietary behavior, and physical activity [4, 5]. Previous research has also provided suggestive evidence that pregnancy and childbirth influence blood pressure and subsequent morbidity and mortality. Pregnancy and childbirth may affect long-term cardiovascular health by several mechanisms, some of which are thought to be protective (elevated estrogen levels during pregnancy [6, 7]), and others of which are thought to increase risk (functional vascular property changes, decreased lipid and glucose metabolism, oxidative stress [8-11], and hemodynamic changes during pregnancy [12]). Further complicating the evaluation of this relationship is the possibility that a subset of nulliparous and nulligravid women did not conceive because of an underlying health issue which may be an independent risk factor for CVD, such as polycystic ovary syndrome and uterine leiomyoma [13, 14].

Studies, largely in populations of European descent, have investigated the association between reproductive history and blood pressure [12, 15-20], but the findings have been equivocal and have not fully addressed the effect of nulliparity and nulligravidity. Studies investigating parity and mortality have also been inconsistent and these studies have differed in study design, sample size, or confounders for which a study adjusted. Two large meta-analyses of cohort studies [21, 22], largely without South Asian participants, suggest J-shaped

associations, with parities of one to six negatively related to all-cause and CVD mortality, and nulliparous women at increased risk. Only one study, using data collected from 1982 to 1998, has examined the effect of parity on all-cause mortality among Bangladeshi women aged 45 to 55 years and observed no association [23].

Given the multiple pathways that may connect reproductive history to morbidity and mortality, it remains unclear whether any associations found in other populations are also valid for the Bangladeshi context as well as other middle-income countries. Therefore, the aim of this study was to evaluate the associations of parity and gravidity with blood pressure and mortality in Bangladeshi women.

METHODS

Study population

The Health Effects of Arsenic Longitudinal Study (HEALS) is an ongoing population-based study in Araihazar, Bangladesh. Between October 2000 and May 2002, we recruited 11 746 participants (5042 males and 6704 females) who met the following eligibility criteria: 1) married couples/individuals (to reduce loss to follow-up); 2) aged 18 to 75 years; 3) users of a tube well as a primary water supply; and, 4) residents of the study area for at least 5 years. During 2006-2008 (ACE I) and 2010-2014 (ACE II), the cohort was expanded to include an additional 8287 (3121 males and 5166 females) and 15 018 participants (5039 males and 9979 females), respectively, in the same study area following the same recruitment methods. Study participants underwent clinical assessment and structured interviews regarding demographic and lifestyle characteristics. More detailed information including study design and data collection can be found elsewhere [24]. Approval of this study was obtained from the Office for the Protection of Research at University of Illinois at Chicago. In the present study, we restricted our analyses to

the 21 634 women (99%) with no missing data on exposures, outcomes, and covariates of interest.

Assessing parity and gravidity

The primary exposure variables are the number of total births (parity) and the number of pregnancies (gravidity). Gravidity, number of livebirths, number of stillbirths, and number of abortions were obtained from the baseline interview. Parity was derived by subtracting the number of abortions from the total number of pregnancies.

Assessing blood pressure

Blood pressure was measured by trained study physicians using an automatic sphygmomanometer with digital display at the baseline [25]. Subjects remained seated for 5 min and blood pressures were taken with the cuff around their upper left arms. After 5 minutes of rest, a second reading was taken and averaged with the first. Participants were asked by trained interviewers to list any medications they were currently taking, and 2.4% (n = 523) reported taking an antihypertensive medication. For those participants, 10 and 5 mmHg were added to their observed systolic and diastolic blood pressures, respectively, to model the magnitude of the potential treatment effect [26]. In subsequent analyses, blood pressure was modeled as a natural log-transformed continuous variable to improve normality. Hypertension was also defined based one the Joint National Committee (JNC) 8 Guideline as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg [27].

Assessing mortality

The vital status of each participant was ascertained by biennial follow-up through June 2017. Follow-up time was calculated as the number of days between the baseline interview and date of death or, if alive, date of the last report of being alive.

A verbal autopsy (VA) procedure, previously validated by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), was implemented to investigate and assign the cause of death for the study participants in the HEALS cohort. In brief, an in-person interview with the informant (relatives or neighbors) of the deceased participant was conducted by a trained study physician to complete the VA questionnaire. If death occurred in the hospital, supplemental documents regarding disease condition prior to death from the hospital, treating physician, or death certificate were obtained. A single cause of death was assigned by a panel of expert physicians. We coded the assigned cause of death based on the World Health Organization's (WHO) tenth revision of the International Classification of Disease (ICD-10) [28]. Deaths due to CVD were deaths classified with ICD-10 codes I00-I99.

Assessing covariates

Participant characteristics including age, years of education, smoking (current, former, never), and land ownership (yes, no) were derived from the baseline interview. BMI was calculated as measured weight in kilograms divided by measured height in meters squared, both measured during the interview.

Statistical analysis

We assessed associations between participant characteristics and parity using analysis of variance for continuous variables and Pearson chi-squared tests for dichotomous variables. Since qualitative examination of the data (**Figure 1**) found no variation in the effects were observed for parity and gravidity of two, three, four, or more, parity and gravidity were subsequently analyzed as three category variables: 0, 1, and ≥ 2.

Blood pressure and hypertension

Linear regression models were used to estimate the % changes and 95% confidence intervals (CIs) in both systolic and diastolic blood pressures. The % change was calculated as $(e^{\beta} - 1) \times 100\%$, with 95% CIs calculated as $(e^{(\beta \pm 1.96 \times SE)} - 1) \times 100\%$. Logistic regression models were used to estimate odds ratios (ORs) and their CIs for the associations of dichotomous hypertension variable with parity and gravidity. Three models were fit: 1) adjusted for cohort (HEALS, ACE I, ACE II); 2) adjusted for cohort and age (years); and, 3) further adjusted including cohort, age, years of education (years), formal education (yes: years of education is not equal to zero, no), land ownership (yes, no), smoking status (current, former, never), BMI (kg/m^2), and number of abortions. Since menopause is an important risk factor for elevated blood pressure [29, 30], the blood pressure analyses were repeated separately for women aged ≤ 45 years (n = 17621) and women aged > 45 years (n = 4013) (menopause status was not available). Arsenic was not included in the analyses since no confounding effect was observed.

Mortality

Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% CIs for the association of parity and gravidity with all-cause mortality and CVD mortality among 4 013 women aged > 45 years. Two models were fit: 1) adjusted for cohort and age; and, 2) further adjusted including cohort, age, years of education, formal education, land ownership, smoking status, BMI (kg/m^2), and number of abortions.

Sensitivity analyses

Three sensitivity analyses were conducted to test the robustness of the analyses. The first sensitivity analysis was conducted restricted to 11 662 women (54%) from the first two recruitment cycles with available information on hormonal contraceptive use since hormonal contraceptive use may also confound the relationship between reproductive history and

cardiovascular health [31]. Of 11 662 women, 26% (n = 3 018) had used hormonal contraceptives. On this subset, the adjusted model was re-run for the blood pressure and hypertension analyses, including current hormonal contraceptive use as an additional covariate. The second sensitivity analysis was performed among women who did not take an antihypertensive medication (n = 21 111). For the last sensitivity analysis, we used another hypertension variable defined based on the 2019 American College of Cardiology and American Heart Association (ACC/AHA) Guideline as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg [32].

Patient and public involvement

There was no patient or public involvement in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Table 1 shows the characteristics of all 21 634 women, overall and by parity. Since gravidity correlated with parity in the present study (r = 0.98), participant characteristics in relation to gravidity are not shown in **Table 1**.The average number of total births was 3.8 (SD = 2.4) with a range of 0 to 15 births and a mode of 2. A total of 605 (2.8%) women were nulliparous. The means of systolic and diastolic blood pressure were 114.4 and 75.0 mmHg, respectively, and the prevalence of hypertension is 5.7%. The mean age of the study participants was 34.9 years. Almost all women in the study were never-smokers. In parous women, increased age, no formal education, tobacco use, and land ownership were associated with higher parity. Furthermore, parity was positively associated with systolic and diastolic blood pressures and prevalence of hypertension.

Table 1. Selected characteristics of 21634 Bangladeshi women in the HEALS cohort

Characteristics	All (N = 21 634)	Total parity			P-value[1]
		0 (n = 605)	1 (n = 2731)	2+ (n = 18 298)	
Systolic BP (mmHg) (mean ± SD)[2]	114.37 (17.07)	113.61 (17.92)	109.83 (12.99)	115.07 (17.46)	<0.0001
Diastolic BP (mmHg) (mean ± SD)[2]	75.01 (10.90)	75.03 (11.01)	71.64 (10.06)	75.50 (10.92)	<0.0001
Hypertension [n (%)]	1239 (5.7)	30 (5.0)	52 (1.9)	1157 (6.3)	<0.0001
Age (year) (mean ± SD)	34.87 (10.67)	28.46 (9.69)	24.73 (6.39)	36.59 (10.28)	<0.0001
Formal education [n (%)]					<0.0001
Yes	12 697 (58.7)	429 (70.9)	2323 (85.1)	9945 (54.4)	
No	8937 (41.3)	176 (29.1)	408 (14.9)	8353 (45.7)	
Land ownership [n (%)]					0.02
Yes	10 167 (47.0)	293 (48.4)	1214 (44.5)	8660 (47.3)	
No	11467 (53.0)	312 (51.2)	1517 (55.6)	9638 (52.7)	
Smoking status [n (%)]					<0.0001
Current	486 (2.3)	11 (1.8)	17 (0.6)	458 (2.5)	
Former	449 (2.1)	4 (0.7)	9 (0.3)	436 (2.4)	
Never	20 669 (95.7)	590 (97.5)	2705 (99.05)	17 404 (95.1)	
BMI (kg/m^2) (mean ± SD)[3]	20.70 (3.57)	21.14 (3.82)	20.85 (3.37)	20.66 (3.59)	0.0004
Number of abortions (mean ± SD)	0.18 (0.50)	0.08 (0.35)	0.15 (0.44)	0.19 (0.51)	<0.0001

[1] Analysis of variance for continuous variable and Pearson Chi-Square test for dichotomous variables

[2] Blood pressure

[3] Body mass index

Association between blood pressure, hypertension, parity, and gravidity

Table 2 summarizes the associations of parity with blood pressure**.** Compared with women with a parity of one, nulliparous women and women with a parity ≥ 2 were more likely to have higher blood pressure in Model 1. The magnitude of the associations changed considerably after adjusting for age (Model 2), suggesting age is an important confounder. The associations were further attenuated when we further adjusted for other confounders (Model 3). Model 3 shows that, overall, women with a parity of one have the lowest blood pressure, and both nulliparous and parity ≥ 2 associate with higher diastolic blood pressure. The confidence intervals of the estimates for systolic blood pressure are consistent with the null, although the magnitude estimates suggest an increase in systolic pressure for nulliparous women. After stratifying at 45 years of age, the associations were attenuated for women aged ≤ 45 years, while larger effect sizes were seen for women aged > 45 years.

Table 2. Crude and adjusted % changes (95% CI) for systolic and diastolic blood pressure according to parity

Parity	Systolic blood pressure			Diastolic blood pressure		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.89 (1.64, 4.16)	1.42 (0.23, 2.62)	1.04 (-0.11, 2.20)	4.76 (3.46, 6.08)	3.62 (2.35, 4.90)	3.12 (1.93, 4.33)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	4.07 (3.49, 4.66)	-0.55 (-1.13, 0.04)	-0.57 (-1.14, -0.00)	5.34 (4.74, 5.94)	1.77 (1.15, 2.39)	1.71 (1.12, 2.31)
Age ≤ 45 (n = 17621)						
0	1.86 (0.68, 3.05)	1.06 (-0.09, 2.22)	0.72 (-0.39, 1.85)	4.18 (2.86, 5.52)	3.21 (1.91, 4.51)	2.78 (1.55, 4.03)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.41 (1.86, 2.95)	-0.24 (-0.83, 0.34)	0.00 (-0.56, 0.57)	4.38 (3.77, 4.99)	1.16 (0.52, 1.80)	1.49 (0.87, 2.11)
Age > 45 (n = 4013)						
0	8.34 (1.87, 15.22)	8.36 (1.92, 15.20)	8.69 (2.52, 15.24)	5.29 (-0.23, 11.11)	5.29 (-0.23, 11.11)	5.67 (0.50, 11.10)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	0.96 (-2.90, 4.97)	0.89 (-2.95, 4.87)	0.68 (-2.98, 4.49)	0.71 (-2.66, 4.20)	0.71 (-2.67, 4.20)	0.57 (-2.57, 3.82)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II)

[2] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)

[3] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Table 3 summarizes the associations of gravidity with blood pressure, which have similar patterns to those observed with parity. While no relationship between gravidity and systolic pressure was found, we observed positive associations of nulligravid and gravidity ≥ 2 with diastolic pressure. As with the parity analysis, we observed stronger relationships for women aged > 45 years, where nulligravidity was associated with higher systolic and diastolic pressures.

Table 3. Crude and adjusted % changes (95% CI) for systolic and diastolic blood pressure according to gravidity

Gravidity	Systolic blood pressure			Diastolic blood pressure		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.82 (1.52, 4.14)	1.22 (-0.02, 2.47)	0.86 (-0.33, 2.07)	4.88 (3.53, 6.25)	3.63 (2.32, 4.96)	3.17 (1.92, 4.43)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	4.03 (3.42, 4.65)	-0.61 (-1.22, -0.00)	-0.67 (-1.26, -0.07)	5.44 (4.81, 6.08)	1.83 (1.19, 2.48)	1.74 (1.12, 2.36)
Age ≤ 45 (n = 17 621)						
0	1.90 (0.68, 3.14)	1.01 (-0.19, 2.22)	0.68 (-0.48, 1.85)	4.40 (3.03, 5.79)	3.31 (1.97, 4.66)	2.89 (1.61, 4.18)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.43 (1.86, 3.00)	-0.24 (-0.83, 0.36)	-0.02 (-0.61, 0.57)	4.50 (3.86, 5.14)	1.25 (0.59, 1.92)	1.54 (0.90, 2.19)
Age > 45 (n = 4013)						
0	4.98 (-1.65, 12.07)	5.05 (-1.56, 12.09)	6.03 (-0.34, 12.81)	3.13 (-2.59, 9.18)	3.13 (-2.59, 9.18)	4.18 (-1.21, 9.87)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	-1.01 (-5.15, 3.31)	-1.09 (-5.21, 3.20)	-1.35 (-5.28, 2.73)	-0.22 (-3.88, 3.57)	-0.22 (-3.88, 3.57)	-0.44 (-3.84, 3.09)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II)
[2] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)
[3] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Table 4 presents the associations of parity and gravidity with hypertension. In model 3, compared with women with a parity of one, nulliparous women had a higher risk of having hypertension. As with the analyses in relation to blood pressure, larger effect estimates were observed for women aged > 45 years, although with confidence intervals that contain zero. No significant associations were observed in relation to gravidity.

Table 4. Crude and adjusted odds ratios (95% CI) of having hypertension according to parity and gravidity

	Parity			Gravidity		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.71 (1.71, 4.28)	1.80 (1.12, 2.87)	1.71 (1.06, 2.75)	2.36 (1.44, 3.86)	1.50 (0.91, 2.49)	1.44 (0.86, 2.39)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	3.54 (2.67, 4.69)	1.27 (0.95, 1.71)	1.25 (0.93, 1.69)	3.44 (2.56, 4.62)	1.21 (0.89, 1.65)	1.18 (0.85, 1.61)
Age ≤ 45 (n = 17621)						
0	1.99 (1.14, 3.47)	1.33 (0.75, 2.34)	1.28 (0.72, 2.27)	2.00 (1.10, 3.63)	1.28 (0.70, 2.34)	1.23 (0.67, 2.27)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.54 (1.86, 3.48)	1.02 (0.73, 1.42)	1.08 (0.77, 1.52)	2.69 (1.91, 3.78)	1.06 (0.73, 1.52)	1.12 (0.78, 1.62)
Age > 45 (n = 4013)						
0	2.48 (0.95, 6.49)	2.48 (0.95, 6.50)	2.67 (0.99, 7.21)	1.18 (0.44, 3.17)	1.18 (0.44, 3.18)	1.34 (0.48, 3.69)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	1.17 (0.58, 2.37)	1.17 (0.58, 2.37)	1.12 (0.54, 2.30)	0.74 (0.38, 1.44)	0.74 (0.38, 1.44)	0.69 (0.35, 1.36)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II)

[2] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)

[3] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

[4] Hypertension defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg based on the Joint National Committee (JNC) 8 Guideline

Association between mortality, parity, and gravidity

We observed 265 deaths (6.6%) among 4 013 women aged > 45 years during the study period [median follow-up time = 8 years (range 5 days to 16.7 years)]. Of this, 101 women (38.1%) died of CVD-related causes and no women died of child birth-related conditions. Since the number of death is not sufficient enough for the analysis in relation to CVD mortality, **Supplemental Table 1** only shows the associations of parity and gravidity with all-cause mortality. Although the confidence intervals were wide and they included the null, elevated risks of all-cause mortality were observed for nulliparity and nulligravidity.

Sensitivity analyses

Sensitivity analysis was conducted to account for the potential confounding effect of hormonal contraceptive use restricted to the 11 662 women (54%) with available data. After additionally adjusting for contraceptive use, the associations of gravidity and parity with blood pressure became stronger, suggesting a negative confounding effect (**Supplemental Table 2**). Similar phenomenon was observed in relation to hypertension (data not shown). For sensitivity analysis performed among 21 111 women who did not take an antihypertensive medication, results were not appreciably different from what we found in our original analyses (**Supplemental Table 3**). Last, we re-performed the analysis in relation to hypertension using the 2019 ACC/AHA Guideline's definition to define hypertensive women. As shown in **Supplemental Table 4**, associations observed using this hypertension variable is stronger as compared to the original hypertension variable defined by JNC 8 Guideline.

DISCUSSION

This analysis finds that in a population of women in rural Bangladesh, nulliparous women and women with a parity ≥ 2 have increased blood pressure, but only nulliparous women shows higher risk of hypertension. These associations were stronger in women > 45 years old. Further, we observed a suggestive higher subsequent mortality among women aged > 45 years old. This study contributes valuable information to the current evidence on the impacts of reproductive history on risk of CVD in a developing country context.

The proportion of women in our study who actively decided to be childfree is unclear, but given the relatively high birth rate in Bangladesh, the proportion of women who are nulliparous or nulligravid due to underlying issues causing infertility may be larger than the proportion of such women in studies from countries with lower birth rates. This may explain why our results suggest a larger risk for nulliparous and nulligravid women than seen in some previous studies.

The associations between reproductive history, blood pressure, and hypertension found in our study are consistent with findings from two large studies based in the US and Korea [12, 15]. However, all of these studies are in contrast to other studies conducted in US populations, which suggested no association [16] or a higher risk of hypertension with each additional birth [18, 19]. The discrepancies may be due to modeling differences, as these studies compared grand parity (≥ 5 births) to low-to-moderate parity without including nulliparous women in the analyses.

Our analysis of parity may help clarify previous contradictory results on mortality. Using data collected from 1982 to 1998, a study among Bangladeshi women aged 45 to 55 years observed no association between parity and all-cause mortality [23]. In contrast, a suggestive elevated risk of mortality in nulliparous women was observed in our analyses. The discrepancy in findings may be due to differences in the study populations across different periods in time. A

recent analysis in US women found a small-increase in all-cause mortality in nulliparous women [33]. Two recent meta-analyses [21, 22] showed that nulliparous women have the highest risk of mortality, which is consistent with our findings. These meta-analyses, however, also found higher risks of all-cause for women with a large number of total births (6-7 births), suggesting a J-shaped relationship between adverse events and parity. Those authors concluded that this may largely arise from behavior-related factors associated with parenting or socioeconomic position (i.e., higher parous women are more likely in lower socioeconomic status). This was not seen in our study possibly reflecting a different relationship between socioeconomic status and parity. In the present study, women with more than five births were much less likely to be educated but more likely to own land. In addition, a few studies included in these meta-analyses did not adjust for age, and this might explain the inconsistency between previous research and our findings. The large difference in the magnitude of the associations observed in the present study suggests that the effect is likely to differ by study populations, sample sizes, and follow-up times.

A potential mechanism by which these effects occur is longer lifetime lactation duration. Lactation has been associated with short-term decreases in blood pressure as well as reduced risk of hypertension and cardiovascular disease in middle age due to potentially lowered stress reactivity from prolonged release of oxytocin [34, 35]. Further, accumulation of fat stores, insulin resistance, and increases in circulating lipid levels are reversed by the mobilization of those fat stores during lactation, with longer duration of lactation supporting more complete reversal of changes [36]. In Bangladesh, the percentage of children breastfed in the second year of life is 92% [37], and thus higher parity would correlate with much longer lifetime lactation duration in this population. While longer duration of breastfeeding may be explained by other maternal health behaviors in developed countries and therefore confound the relationship with

cardiovascular health [34], this is likely not the case in Bangladesh where long duration of breastfeeding is the norm.

This study has limitations that should be considered. First, since childbearing history was self-reported and menopause status was not ascertained, misclassification could have occurred. Even assuming some misclassification of menopausal status, the large changes in magnitude observed in the age-stratified analyses suggest that, on average, women over 45 years have a different relationship between reproductive history and hypertensive morbidity and mortality than younger women. Additionally, some unmeasured confounders may remain unaccounted for in our statistical analyses. Lastly, understanding lactation's effect within this relationship and independently could be explored to expand our understanding of maternal health benefits associated with lactation in developing countries.

In conclusion, we have investigated the effects of pregnancy and childbirth on blood pressure and mortality and found that nulliparous and nulligravid women have the highest risk of having hypertension. We also observed a modest increase in diastolic blood pressure for parity and gravidity numbers greater than two. Future studies in populations with similar socioeconomic backgrounds and patterns of fertility are needed to confirm current findings.

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Declaration of interest: There are no competing interests for any author.

Contributors: Maria Argos, Faruque Parvez, and Habibul Ahsan designed the study and directed its implementation, including quality assurance and control. Mohammed Shahriar, Alauddin Ahmed, and Tariqul Islam helped supervise the field activities. Yu-Hsuan Shih, Molly Scannell Bryan, and Maria Argos designed the study's analytic strategy. Yu-Hsuan Shih, Molly Scannell Bryan, Keriann Hunter Uesugi, and Maria Argos helped conduct the literature review and prepare the Methods and the Discussion sections of the text.

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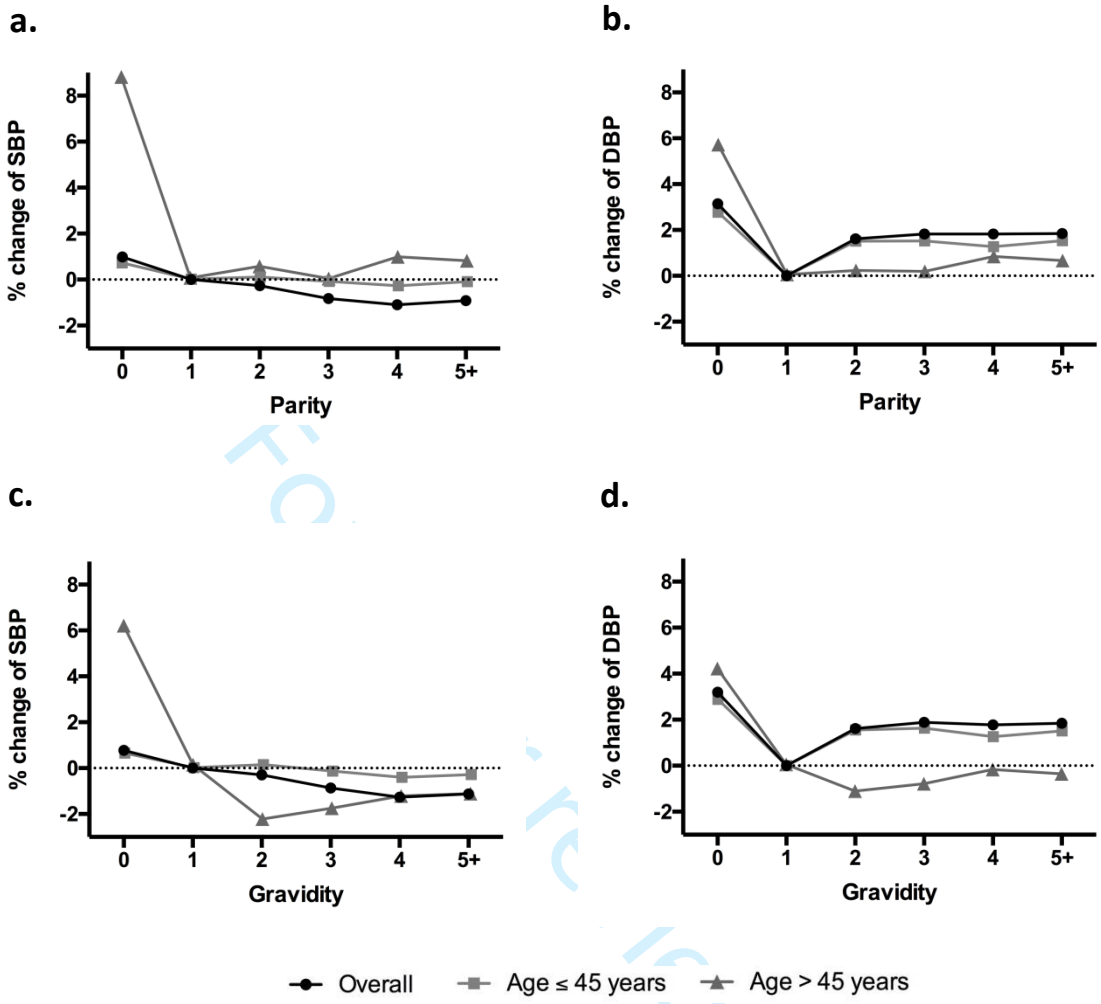
Figure 1. Adjusted % change for the association between reproductive history and blood pressure, overall, and stratified on 45-years of age: a) parity and systolic blood pressure (SBP); b) parity and diastolic blood pressure (DBP); c) gravidity and SBP; and d) gravidity and DBP

Author's contribution

Maria Argos, Faruque Parvez, and Habibul Ahsan designed the study and directed its implementation, including quality assurance and control. Mohammed Shahriar, Alauddin Ahmed, and Tariqul Islam helped supervise the field activities. Yu-Hsuan Shih, Molly Scannell Bryan, and Maria Argos designed the study's analytic strategy. Yu-Hsuan Shih, Molly Scannell Bryan, Keriann Hunter Uesugi, and Maria Argos helped conduct the literature review and prepare the Methods and the Discussion sections of the text.



Supplemental Table 1. Adjusted hazard ratio (95% CI) for the association of gravidity and parity with mortality among 4013 women aged > 45 years in Bangladesh

	All-cause mortality	
	Model 1[1]	Model 2[2]
Parity		
0	4.00 (0.78, 20.59)	3.83 (0.74, 19.78)
1	Ref	Ref
2+	0.87 (0.57, 1.32)	1.90 (0.47, 7.65)
Gravidity		
0	3.58 (0.69, 18.43)	3.37 (0.65, 17.40)
1	Ref	Ref
2+	1.56 (0.39, 6.26)	1.57 (0.39, 6.34)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)
[1] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), BMI (kg/m^2), and number of abortions

Supplemental table 2. Adjusted % changes (95% CI) for systolic and diastolic blood pressure according to parity, restricting to 11 662 women with information on hormonal contraceptive (HC) use

	Systolic blood pressure		Diastolic blood pressure	
	Adjusted[1]	Adjusted + HC	Adjusted[1]	Adjusted + HC
Parity				
0	2.35 (0.58, 4.15)	2.82 (1.04, 4.63)	3.90 (2.08, 5.76)	4.34 (2.50, 6.20)
1	Ref	Ref	Ref	Ref
2+	0.02 (-0.87, 0.92)	-0.35 (-1.24, 0.54)	2.46 (1.53, 3.39)	2.11 (1.19, 3.04)
Gravidity				
0	2.15 (0.33, 4.00)	2.61 (0.78, 4.47)	3.74 (1.86, 5.64)	4.15 (2.27, 6.07)
1	Ref	Ref	Ref	Ref
2+	-0.04 (-0.97, 0.89)	-0.41 (-1.34, 0.52)	2.53 (1.57, 3.51)	2.19 (1.22, 3.16)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Supplemental table 3. Adjusted % changes (95% CI) for systolic and diastolic blood pressure according to parity, restricting to 21 111 women without taking an antihypertensive medication

	Systolic blood pressure			Diastolic blood pressure		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Parity						
0	2.47 (1.27, 3.69)	1.34 (0.18, 2.52)	0.99 (-0.13, 2.13)	4.37 (3.09, 5.67)	3.48 (2.23, 4.75)	3.02 (1.83, 4.22)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	3.48 (2.92, 4.04)	-0.29 (-0.85, 0.28)	-0.34 (-0.89, 0.22)	4.89 (4.30, 5.48)	1.93 (1.32, 2.54)	1.84 (1.25, 2.44)
Gravidity						
0	2.50 (1.25, 3.76)	1.23 (0.03, 2.45)	0.91 (-0.26, 2.09)	4.55 (3.23, 5.90)	3.55 (2.25, 4.87)	3.12 (1.88, 4.37)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	3.46 (2.88, 4.05)	-0.33 (-0.92, 0.26)	-0.40 (-0.98, 0.18)	5.00 (4.38, 5.62)	2.00 (1.36, 2.64)	1.88 (1.26, 2.50)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II)
[2] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)
[3] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Supplemental Table 4. Crude and adjusted odds ratios (95% CI) of having hypertension[4] according to parity and gravidity

	Parity			Gravidity		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.66 (1.99, 3.56)	1.96 (1.46, 2.65)	1.87 (1.38, 2.54)	2.49 (1.84, 3.38)	1.78 (1.30, 2.43)	1.70 (1.23, 2.33)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	3.14 (2.64, 3.73)	1.36 (1.13, 1.63)	1.34 (1.11, 1.62)	3.05 (2.55, 3.66)	1.30 (1.07, 1.57)	1.27 (1.05, 1.55)
Age ≤ 45 (n = 17621)						
0	2.18 (1.57, 3.01)	1.72 (1.23, 2.39)	1.64 (1.17, 2.29)	2.14 (1.52, 3.00)	1.64 (1.15, 2.32)	1.56 (1.10, 2.22)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.32 (1.93, 2.79)	1.24 (1.02, 1.51)	1.28 (1.05, 1.57)	2.34 (1.92, 2.84)	1.23 (1.00, 1.51)	1.28 (1.04, 1.58)
Age > 45 (n = 4013)						
0	3.46 (1.52, 7.89)	3.48 (1.52, 7.94)	3.96 (1.68, 9.35)	1.96 (0.85, 4.52)	1.98 (0.86, 4.56)	2.29 (0.96, 5.46)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	1.67 (0.93, 3.02)	1.67 (0.92, 3.01)	1.67 (0.92, 3.07)	1.10 (0.62, 1.96)	1.10 (0.61, 1.96)	1.05 (0.57, 1.91)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II)

[2] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)

[3] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

[4] Hypertension defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg based on the 2017 American College of Cardiology and American Heart Association (ACC/AHA) Guideline

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups. (Not applicable to this study)

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Gravidity, parity, blood pressure, and mortality among women in Bangladesh from the HEALS cohort

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Data availability: Data are available upon reasonable request and on approval from the project principal investigator.

Abstract

Objectives: Despite a hypothesized connection of reproductive history with hypertension and mortality, the nature of this association is poorly characterized. We evaluated the association of parity and gravidity with blood pressure, hypertension, and all-cause mortality.

Design: Prospective cohort study.

Setting: Health Effects of Arsenic Longitudinal Study (HEALS) cohort in rural Bangladesh

Paticipants: There were 21 634 Bangladeshi women recruited in 2000-2002, 2006-2008, and 2010-2014 included in the present analysis.

Methods: Reproductive history was ascertained through an interviewer-administered questionnaire at the baseline visit. Blood pressure was measured by a trained study physician following a standard protocol at the baseline visit. Vital status was ascertained at the biennial follow-up of study participants through June 2017. Linear and logistic regression models estimated the relationship between parity and gravidity with blood pressure and hypertension, respectively. Cox proportional hazards models estimated the relationship with all-cause mortality only among women aged > 45 years.

Results: Diastolic blood pressure was lowest in women with parity one (reference) and elevated in nulliparous women (adjusted % change = 3.12; 95% CI: 1.93, 4.33) and women with parity ≥ 2 (adjusted % change = 1.71; 95% CI: 1.12, 2.31). The associations with nulliparity were stronger for women aged > 45 years. Similar association patterns were observed with hypertension. Further, in nulliparous women aged > 45 years, 265 deaths (6.6%) were ascertained during the follow-up period (median follow-up time = 8 years), and we observed suggestive elevated risks of all-cause mortality (adjusted HR = 3.83; 95% CI: 0.74, 19.78). The

relationships between reproductive history, blood pressure, hypertension, and mortality were similar when modeling reproductive history as gravidity rather than parity.

Conclusions: For women in rural Bangladesh, nulliparity and nulligravidity appear to be associated with higher blood pressure and subsequent elevated risk of mortality

Keywords: Public health, epidemiology, hypertension

Strength and limitations of this study

- Large, rigorously conducted prospective cohort study in a developing country context.
- Childbearing history was self-reported and menopause status was not ascertained.
- Unmeasured confounders may remain unaccounted for in our analyses.

INTRODUCTION

Elevated blood pressure is an established risk factor for cardiovascular diseases (CVDs) (1, 2), and complications of hypertension account for approximately 9.4 million deaths worldwide (3). In Bangladesh, as in other South Asian countries, hypertension is a significant health concern with an overall prevalence of 26.4% among adults, with a higher prevalence (32.4%) in women (4).

A woman's risk for developing hypertension is influenced by several factors, including age, body mass index (BMI), menopause, dietary behavior, and physical activity (4, 5). Previous research has also provided suggestive evidence that pregnancy and childbirth influence blood pressure and subsequent morbidity and mortality. Pregnancy and childbirth may affect long-term cardiovascular health by several mechanisms, some of which are thought to be protective (elevated estrogen levels during pregnancy (6, 7)), and others of which are thought to increase risk (functional vascular property changes, decreased lipid and glucose metabolism, oxidative stress (8-11), and hemodynamic changes during pregnancy (12)). Further complicating the evaluation of this relationship is the possibility that a subset of nulliparous and nulligravid women did not conceive because of an underlying health issue, which may be an independent risk factor for CVD, such as polycystic ovary syndrome and uterine leiomyoma (13, 14).

Studies, largely in populations of European descent, have investigated the association between reproductive history and blood pressure (12, 15-21). Still, the findings have been equivocal and have not adequately addressed the effect of nulliparity and nulligravidity. Studies investigating parity and mortality have also been inconsistent, and these studies have differed in study design, sample size, or confounders for which a study adjusted (22-27). Two large meta-analyses of cohort studies (26, 27), largely without South Asian participants, suggest J-shaped

associations, with parities of one to six negatively related to all-cause and CVD mortality, and nulliparous women at increased risk. Only one study, using data collected from 1982 to 1998, has examined the effect of parity on all-cause mortality among Bangladeshi women aged 45 to 55 years and observed no association (28).

Given the multiple pathways that may connect reproductive history to morbidity and mortality, it remains unclear whether any associations found in other populations are also valid for the Bangladeshi context as well as other middle-income countries. Therefore, this study aimed to evaluate the associations of parity and gravidity with blood pressure and mortality in Bangladeshi women.

METHODS

Study population

The Health Effects of Arsenic Longitudinal Study (HEALS) is an ongoing population-based study in Araihazar, Bangladesh. Between October 2000 and May 2002, we recruited 11 746 participants (5042 males and 6704 females) who met the following eligibility criteria: 1) married couples/individuals (to reduce loss to follow-up); 2) aged 18 to 75 years; 3) users of a tube well as a primary water supply; and, 4) residents of the study area for at least 5 years. During 2006-2008 (ACE I) and 2010-2014 (ACE II), the cohort was expanded to include an additional 8287 (3121 males and 5166 females) and 15 018 participants (5039 males and 9979 females), respectively, in the same study area following the same recruitment methods. Study participants underwent clinical assessment and face-to-face structured interviews regarding demographic and lifestyle characteristics. More detailed information, including study design and data collection, can be found elsewhere (29). The study protocol was approved by the institutional review boards of The University of Chicago, Columbia University, the University of Illinois at Chicago, and

the Bangladesh Medical Research Council. In the present study, we restricted our analyses to the 21 634 women (99%) with no missing data on exposures, outcomes, and covariates of interest.

Assessing parity and gravidity

The primary exposure variables are the number of total births (parity) and the number of pregnancies (gravidity). Gravidity, number of livebirths, number of stillbirths, and number of abortions were obtained from the interviewer-administered baseline questionnaire. Parity was derived by subtracting the number of abortions from the total number of pregnancies.

Assessing blood pressure

Blood pressure was measured by a trained study physician using an automated sphygmomanometer with a digital display at the baseline visit (30). Subjects remained seated for 5 min, and blood pressures were taken with the cuff around their upper left arms. After 5 minutes of rest, a second reading was taken and averaged with the first. Participants were asked by trained interviewers to list any medications they were currently taking, and 2.4% (n = 523) reported taking antihypertensive medication. For those participants, 10 and 5 mmHg were added to their observed systolic and diastolic blood pressures, respectively, to account for the magnitude of the potential treatment effect (31). In subsequent analyses, blood pressure was modeled as a natural log-transformed continuous variable to improve normality. Hypertension was also defined based on the Joint National Committee (JNC) 8 Guideline as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg (32).

Assessing mortality

The vital status of each participant was ascertained at biennial follow-up visits through June 2017. Follow-up time was calculated as the number of days between the baseline visit and date of death or, if alive, the date of the last report of being alive.

A verbal autopsy (VA) procedure, previously validated by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), was implemented to investigate and assign the cause of death for the study participants in the HEALS cohort. In brief, an in-person interview with the informant (relatives or neighbors) of the deceased participant was conducted by a trained study physician to complete the VA questionnaire. If the death occurred in the hospital, supplemental documents regarding disease condition prior to death from the hospital, treating physician, or death certificate were obtained. A panel of expert physicians assigned a single cause of death. We coded the assigned cause of death based on the World Health Organization's (WHO) tenth revision of the International Classification of Disease (ICD-10) (33). Deaths classified with ICD-10 codes I00-I99 were attributed to CVD.

Assessing covariates

Self-reported participant characteristics including age, years of education, occupation (daily laborer/farmer, factory worker, business, homemaker, other), smoking status (current, former, never), and land ownership (yes, no) were derived from the baseline interviewer-administered questionnaire. BMI was calculated as measured weight in kilograms divided by measured height in meters squared; a trained study physician measured both during the baseline interview following a standard protocol.

Statistical analysis

We assessed associations between participant characteristics and parity using analysis of variance for continuous variables and Pearson chi-squared tests for dichotomous variables. Since qualitative examination of the data (**Figure 1**) revealed no variation in the observed effects for parity and gravidity of two, three, four, or more, parity and gravidity were subsequently analyzed as three category variables: 0, 1, and ≥ 2.

Blood pressure and hypertension

Linear regression models were used to estimate the % changes and 95% confidence intervals (CIs) in both systolic and diastolic blood pressures. The % change was calculated as $(e^{\beta} - 1) \times 100\%$, with 95% CIs calculated as $(e^{(\beta \pm 1.96 \times SE)} - 1) \times 100\%$. Logistic regression models were used to estimate odds ratios (ORs) and their CIs for the associations of the dichotomous hypertension variable with parity and gravidity. Three models were fit: 1) adjusted for cohort (HEALS, ACE I, ACE II); 2) adjusted for cohort and age (years); and, 3) adjusted for cohort, age, years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (current, former, never), and BMI (kg/m^2). Since menopause is an important risk factor for elevated blood pressure (34, 35), the blood pressure analyses were repeated separately for women aged ≤ 45 years (n = 17621) and women aged > 45 years (n = 4013) since menopause status was not available. Arsenic was not included in the analyses since no confounding effect was observed.

Mortality

Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% CIs for the association of parity and gravidity with all-cause mortality and CVD mortality among 4 013 women aged > 45 years. Two models were fit: 1) adjusted for cohort and age; and 2) further adjusted including cohort, age, years of education, formal education, land ownership, smoking status, and BMI (kg/m^2), and number of abortions.

Sensitivity analyses

Three sensitivity analyses were conducted to test the robustness of the analyses. The first sensitivity analysis was conducted restricted to 11 662 women (54%) from the first two recruitment cycles with available information on hormonal contraceptive use since hormonal

contraceptive use may also confound the relationship between reproductive history and cardiovascular health (36). Of 11 662 women, 26% (n = 3 018) had used hormonal contraceptives. On this subset, the adjusted model was re-run for the blood pressure and hypertension analyses, including current hormonal contraceptive use as an additional covariate. The second sensitivity analysis was performed among women who did not take antihypertensive medication (n = 21 111). In the third sensitivity analysis, we defined hypertension based on the 2019 American College of Cardiology and American Heart Association (ACC/AHA) Guideline as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg (37).

Patient and public involvement

There was no patient or public involvement in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Table 1 shows the characteristics of all 21 634 women, overall and by parity. Since gravidity correlated with parity in the present study (r = 0.98), participant characteristics in relation to gravidity are not shown in **Table 1**. The average number of total births was 3.8 (SD = 2.4), with a range of 0 to 15 births and a mode of 2. A total of 605 (2.8%) women were nulliparous. The means of systolic and diastolic blood pressure were 114.4 and 75.0 mmHg, respectively, and the prevalence of hypertension was 5.7%. The mean age of the study participants was 34.9 years (range: 18-65 years). Almost all women in the study were never-smokers. In parous women, increased age, no formal education, tobacco use, and land ownership were associated with higher parity. Furthermore, parity was positively associated with systolic and diastolic blood pressures and the prevalence of hypertension.

Table 1. Selected characteristics of 21634 Bangladeshi women in the HEALS cohort

Characteristics	All (N = 21 634)	Total parity			P-value[1]
		0 (n = 605)	1 (n = 2731)	2+ (n = 18 298)	
Systolic BP (mmHg) (mean ± SD)[2]	114.37 (17.07)	113.61 (17.92)	109.83 (12.99)	115.07 (17.46)	<0.0001
Diastolic BP (mmHg) (mean ± SD)[2]	75.01 (10.90)	75.03 (11.01)	71.64 (10.06)	75.50 (10.92)	<0.0001
Hypertension [n (%)]	1239 (5.7)	30 (5.0)	52 (1.9)	1157 (6.3)	<0.0001
Age (year) (mean ± SD)	34.87 (10.67)	28.46 (9.69)	24.73 (6.39)	36.59 (10.28)	<0.0001
Formal education [n (%)]					<0.0001
Yes	12 697 (58.7)	429 (70.9)	2323 (85.1)	9945 (54.4)	
No	8937 (41.3)	176 (29.1)	408 (14.9)	8353 (45.7)	
Land ownership [n (%)]					0.02
Yes	10 167 (47.0)	293 (48.4)	1214 (44.5)	8660 (47.3)	
No	11 467 (53.0)	312 (51.2)	1517 (55.6)	9638 (52.7)	
Occupation [n (%)]					0.04
Daily laborer/farmer	46 (0.2)	1 (0.2)	3 (0.1)	42 (0.2)	
Factory worker	741 (3.4)	15 (2.5)	82 (3.0)	644 (3.5)	
Business	403 (1.9)	9 (1.5)	62 (2.3)	332 (1.8)	
Homemaker	19 845 (91.7)	553 (91.4)	2500 (91.5)	16 792 (91.8)	
Other	599 (2.7)	27 (4.4)	84 (3.0)	488 (2.7)	
Smoking status [n (%)]					<0.0001
Current	486 (2.3)	11 (1.8)	17 (0.6)	458 (2.5)	
Former	449 (2.1)	4 (0.7)	9 (0.3)	436 (2.4)	
Never	20 669 (95.7)	590 (97.5)	2705 (99.05)	17 404 (95.1)	
BMI (kg/m^2) (mean ± SD)[3]	20.70 (3.57)	21.14 (3.82)	20.85 (3.37)	20.66 (3.59)	0.0004
Number of abortions (mean ± SD)	0.18 (0.50)	0.08 (0.35)	0.15 (0.44)	0.19 (0.51)	<0.0001

[1] Analysis of variance for continuous variable and Pearson chi-squared test for dichotomous variables

[2] Blood pressure

[3] Body mass index

Association between blood pressure, hypertension, parity, and gravidity

Table 2 summarizes the associations of parity with blood pressure**.** Compared with women with a parity of one, nulliparous women and women with a parity ≥ 2 were more likely to have higher blood pressure in Model 1. The magnitude of the associations changed considerably after adjusting for age (Model 2), suggesting age is an important confounder. The associations were further attenuated when we additionally adjusted for other confounders (Model 3). Model 3 shows that, overall, women with a parity of one have the lowest blood pressure, and both nulliparous and parity ≥ 2 associate with higher diastolic blood pressure. The confidence intervals of the estimates for systolic blood pressure are consistent with the null, although the magnitude of the estimates suggests an increase in systolic pressure for nulliparous women. After stratifying at 45 years of age, the associations with nulliparity were attenuated for women aged ≤ 45 years, while larger effect sizes were seen for women aged > 45 years.

Table 2. Crude and adjusted % changes (95% CI) for systolic and diastolic blood pressure according to parity

Parity	Systolic blood pressure			Diastolic blood pressure		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.89 (1.64, 4.16)	1.42 (0.23, 2.62)	1.04 (-0.11, 2.20)	4.76 (3.46, 6.08)	3.62 (2.35, 4.90)	3.12 (1.93, 4.33)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	4.07 (3.49, 4.66)	-0.55 (-1.13, 0.04)	-0.57 (-1.14, -0.00)	5.34 (4.74, 5.94)	1.77 (1.15, 2.39)	1.71 (1.12, 2.31)
Age ≤ 45 (n = 17621)						
0	1.86 (0.68, 3.05)	1.06 (-0.09, 2.22)	0.72 (-0.39, 1.85)	4.18 (2.86, 5.52)	3.21 (1.91, 4.51)	2.78 (1.55, 4.03)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.41 (1.86, 2.95)	-0.24 (-0.83, 0.34)	0.00 (-0.56, 0.57)	4.38 (3.77, 4.99)	1.16 (0.52, 1.80)	1.49 (0.87, 2.11)
Age > 45 (n = 4013)						
0	8.34 (1.87, 15.22)	8.36 (1.92, 15.20)	8.69 (2.52, 15.24)	5.29 (-0.23, 11.11)	5.29 (-0.23, 11.11)	5.67 (0.50, 11.10)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	0.96 (-2.90, 4.97)	0.89 (-2.95, 4.87)	0.68 (-2.98, 4.49)	0.71 (-2.66, 4.20)	0.71 (-2.67, 4.20)	0.57 (-2.57, 3.82)

[1] Adjusted for cohort (HEALS, ACE I, ACE II)

[2] Adjusted for cohort (HEALS, ACE I, ACE II) and age (years)

[3] Adjusted for cohort (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Table 3 summarizes the associations of gravidity with blood pressure, which have similar patterns to those observed with parity. While no relationship between gravidity and systolic blood pressure was found, we observed positive associations of nulligravid and gravidity ≥ 2 with diastolic blood pressure. As with the parity analysis, we observed stronger relationships for women aged > 45 years, where nulligravidity was associated with higher systolic and diastolic pressures.

Table 3. Crude and adjusted % changes (95% CI) for systolic and diastolic blood pressure according to gravidity

Gravidity	Systolic blood pressure			Diastolic blood pressure		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.82 (1.52, 4.14)	1.22 (-0.02, 2.47)	0.86 (-0.33, 2.07)	4.88 (3.53, 6.25)	3.63 (2.32, 4.96)	3.17 (1.92, 4.43)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	4.03 (3.42, 4.65)	-0.61 (-1.22, -0.00)	-0.67 (-1.26, -0.07)	5.44 (4.81, 6.08)	1.83 (1.19, 2.48)	1.74 (1.12, 2.36)
Age ≤ 45 (n = 17 621)						
0	1.90 (0.68, 3.14)	1.01 (-0.19, 2.22)	0.68 (-0.48, 1.85)	4.40 (3.03, 5.79)	3.31 (1.97, 4.66)	2.89 (1.61, 4.18)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.43 (1.86, 3.00)	-0.24 (-0.83, 0.36)	-0.02 (-0.61, 0.57)	4.50 (3.86, 5.14)	1.25 (0.59, 1.92)	1.54 (0.90, 2.19)
Age > 45 (n = 4013)						
0	4.98 (-1.65, 12.07)	5.05 (-1.56, 12.09)	6.03 (-0.34, 12.81)	3.13 (-2.59, 9.18)	3.13 (-2.59, 9.18)	4.18 (-1.21, 9.87)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	-1.01 (-5.15, 3.31)	-1.09 (-5.21, 3.20)	-1.35 (-5.28, 2.73)	-0.22 (-3.88, 3.57)	-0.22 (-3.88, 3.57)	-0.44 (-3.84, 3.09)

[1] Adjusted for cohort (HEALS, ACE I, ACE II)
[2] Adjusted for cohort (HEALS, ACE I, ACE II) and age (years)
[3] Adjusted for cohort (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Table 4 presents the associations of parity and gravidity with hypertension. In model 3, nulliparous women had a higher risk of having hypertension compared with women with a parity of one. As with the analyses in relation to blood pressure, larger effect estimates were observed for women aged > 45 years, although the confidence intervals contained the null. No significant associations were observed in relation to gravidity.

Table 4. Crude and adjusted odds ratios (95% CI) of having hypertension according to parity and gravidity

	Parity			Gravidity		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.71 (1.71, 4.28)	1.80 (1.12, 2.87)	1.71 (1.06, 2.75)	2.36 (1.44, 3.86)	1.50 (0.91, 2.49)	1.44 (0.86, 2.39)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	3.54 (2.67, 4.69)	1.27 (0.95, 1.71)	1.25 (0.93, 1.69)	3.44 (2.56, 4.62)	1.21 (0.89, 1.65)	1.18 (0.85, 1.61)
Age ≤ 45 (n = 17621)						
0	1.99 (1.14, 3.47)	1.33 (0.75, 2.34)	1.28 (0.72, 2.27)	2.00 (1.10, 3.63)	1.28 (0.70, 2.34)	1.23 (0.67, 2.27)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.54 (1.86, 3.48)	1.02 (0.73, 1.42)	1.08 (0.77, 1.52)	2.69 (1.91, 3.78)	1.06 (0.73, 1.52)	1.12 (0.78, 1.62)
Age > 45 (n = 4013)						
0	2.48 (0.95, 6.49)	2.48 (0.95, 6.50)	2.67 (0.99, 7.21)	1.18 (0.44, 3.17)	1.18 (0.44, 3.18)	1.34 (0.48, 3.69)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	1.17 (0.58, 2.37)	1.17 (0.58, 2.37)	1.12 (0.54, 2.30)	0.74 (0.38, 1.44)	0.74 (0.38, 1.44)	0.69 (0.35, 1.36)

[1] Adjusted for cohort (HEALS, ACE I, ACE II)

[2] Adjusted for cohort (HEALS, ACE I, ACE II) and age (years)

[3] Adjusted for cohort (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

[4] Hypertension defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg based on the Joint National Committee (JNC) 8 Guideline

Association between mortality, parity, and gravidity

We observed 265 deaths (6.6%) among 4 013 women aged > 45 years during the study period [median follow-up time = 8 years (range 5 days to 16.7 years)]. Of this, 101 women (38.1%) died of CVD-related causes, and no women died of childbirth-related conditions. Since the number of deaths was not sufficient to conduct analysis in relation to CVD mortality, **Supplemental Table 1** shows the associations of parity and gravidity with all-cause mortality. Although the confidence intervals were wide, and they included the null, elevated risks of all-cause mortality were observed for nulliparity and nulligravidity.

Sensitivity analyses

A sensitivity analysis was conducted to account for the potential confounding effect of hormonal contraceptive use restricted to the 11 662 women (54%) with available data. After additionally adjusting for contraceptive use, the associations of gravidity and parity with blood pressure became stronger, suggesting a negative confounding effect (**Supplemental Table 2**). A similar phenomenon was observed in relation to hypertension (data not shown). For the sensitivity analysis performed among 21 111 women who did not take antihypertensive medication, results were not appreciably different from what we found in our original analyses (**Supplemental Table 3**). Last, we performed the analysis in relation to hypertension using the 2019 ACC/AHA Guideline to define hypertensive women. As shown in **Supplemental Table 4**, associations observed using this hypertension definition were stronger as compared to the original hypertension variable defined by the JNC 8 Guideline.

DISCUSSION

This analysis finds that in a population of women in rural Bangladesh, nulliparous women and women with a parity ≥ 2 have increased blood pressure, but only nulliparous women were observed to have a higher risk of hypertension. The associations with nulliparity were stronger in women > 45 years old. Furthermore, there was suggestive evidence of higher subsequent mortality among nulliparous women aged > 45 years old. This study contributes valuable information to the current evidence on the impacts of reproductive history on the risk of CVD in a developing country context.

The proportion of women in our study who actively decided not to have children is unclear, but given the relatively high birth rate in Bangladesh, the proportion of women who are nulliparous or nulligravid due to underlying issues causing infertility may be larger than the proportion of such women in studies from countries with lower birth rates. This may explain why our results suggest a larger risk for nulliparous and nulligravid women than seen in some previous studies.

The associations between reproductive history, blood pressure, and hypertension found in our study are consistent with findings from three large studies based in the US, Korea, and Norway (12, 15, 21). However, all of these studies are in contrast to other studies conducted in US populations, which suggested no association (16) or a higher risk of hypertension with each additional birth (18, 19). The discrepancies may be due to modeling differences, as these studies compared grand parity (≥ 5 births) to low-to-moderate parity without including nulliparous women in the analyses.

Our analysis of parity may help clarify previous contradictory results on mortality. Using data collected from 1982 to 1998, a study among Bangladeshi women aged 45 to 55 years

observed no association between parity and all-cause mortality (28). Another study of 518 Amish women with a mean age of 63.1 years also reported no association between parity and mortality (25). In contrast, a suggestive elevated risk of mortality in nulliparous women was observed in our analyses. The discrepancy in findings may be due to differences in the study populations across different periods in time. A recent analysis in US women found a small increase in all-cause mortality in nulliparous women (24). Two recent meta-analyses (26, 27) and a Japanese cohort study (22) showed that nulliparous women have the highest risk of mortality, which is consistent with our findings. These studies, however, also found higher risks of all-cause or CVD mortality for women with a large number of total births (6-7 births), suggesting a J-shaped relationship between mortality and parity. The authors concluded that this might largely arise from behavior-related factors associated with parenting or socioeconomic position (i.e., higher parous women are more likely to have lower socioeconomic status). This was not seen in our study, possibly reflecting a different relationship between socioeconomic status and parity in rural Bangladesh. In the present study, women with more than five births were much less likely to have a formal education but more likely to own land. In addition, a few studies included in these meta-analyses did not adjust for age, and this might explain the inconsistency between previous research and our findings. The large difference in the magnitude of the associations observed in the present study suggests that the effect is likely to differ by study populations, sample sizes, and follow-up times.

A potential mechanism by which these effects occur is longer lifetime lactation duration. Lactation has been associated with short-term decreases in blood pressure as well as reduced risk of hypertension and cardiovascular disease in middle age due to potentially lowered stress reactivity from the prolonged release of oxytocin (38, 39). Further, accumulation of fat stores,

insulin resistance, and increases in circulating lipid levels are reversed by the mobilization of those fat stores during lactation, with longer duration of lactation supporting more complete reversal of changes (40). In Bangladesh, the percentage of children breastfed in the second year of life is 92% (41), and thus higher parity would correlate with much longer lifetime lactation duration in this population. While longer duration of breastfeeding may be explained by other maternal health behaviors in developed countries and therefore confound the relationship with cardiovascular health (38), this is likely not the case in Bangladesh where long duration of breastfeeding is the norm.

The present study has limitations that should be considered. First, since reproductive history was self-reported at the baseline visit, there is the possibility for misclassification of parity and gravidity, particularly among older women; however, we deem that self-reported parity is both reliable and valid (42). Additionally, menopausal status was not ascertained, and thus age was used as a proxy, which may have resulted in some misclassification. Even assuming some misclassification of menopausal status, the large changes in magnitude observed in the age-stratified analyses suggest that, on average, women over 45 years have a different relationship between reproductive history and hypertensive morbidity and mortality than younger women. Additionally, some unmeasured confounders, such as gestational weight gain (only a consideration for the findings related to parous women) (43, 44), underlying health issues (e.g., polycystic ovary syndrome and uterine leiomyoma), and other socioeconomic status-related variables (e.g., income), were not collected and remain unaccounted for in our statistical analyses. Lastly, understanding the effect of lactation on this relationship and independently could be explored to expand our understanding of maternal health benefits associated with lactation in developing countries.

In conclusion, we have investigated the effects of pregnancy and childbirth on blood pressure and mortality and found that nulliparous and nulligravid women have the highest risk of hypertension. We also observed a modest increase in diastolic blood pressure for parity and gravidity higher than two. Future studies in populations with similar socioeconomic backgrounds and patterns of fertility are needed to confirm current findings.

Contributors: Maria Argos, Faruque Parvez, and Habibul Ahsan designed the study and directed its implementation, including quality assurance and control. Mohammed Shahriar, Alauddin Ahmed, and Tariqul Islam helped supervise the field activities. Yu-Hsuan Shih, Molly Scannell Bryan, and Maria Argos designed the study's analytic strategy. Yu-Hsuan Shih, Molly Scannell Bryan, Keriann Hunter Uesugi, and Maria Argos helped conduct the literature review and prepare the Methods and the Discussion sections of the text.

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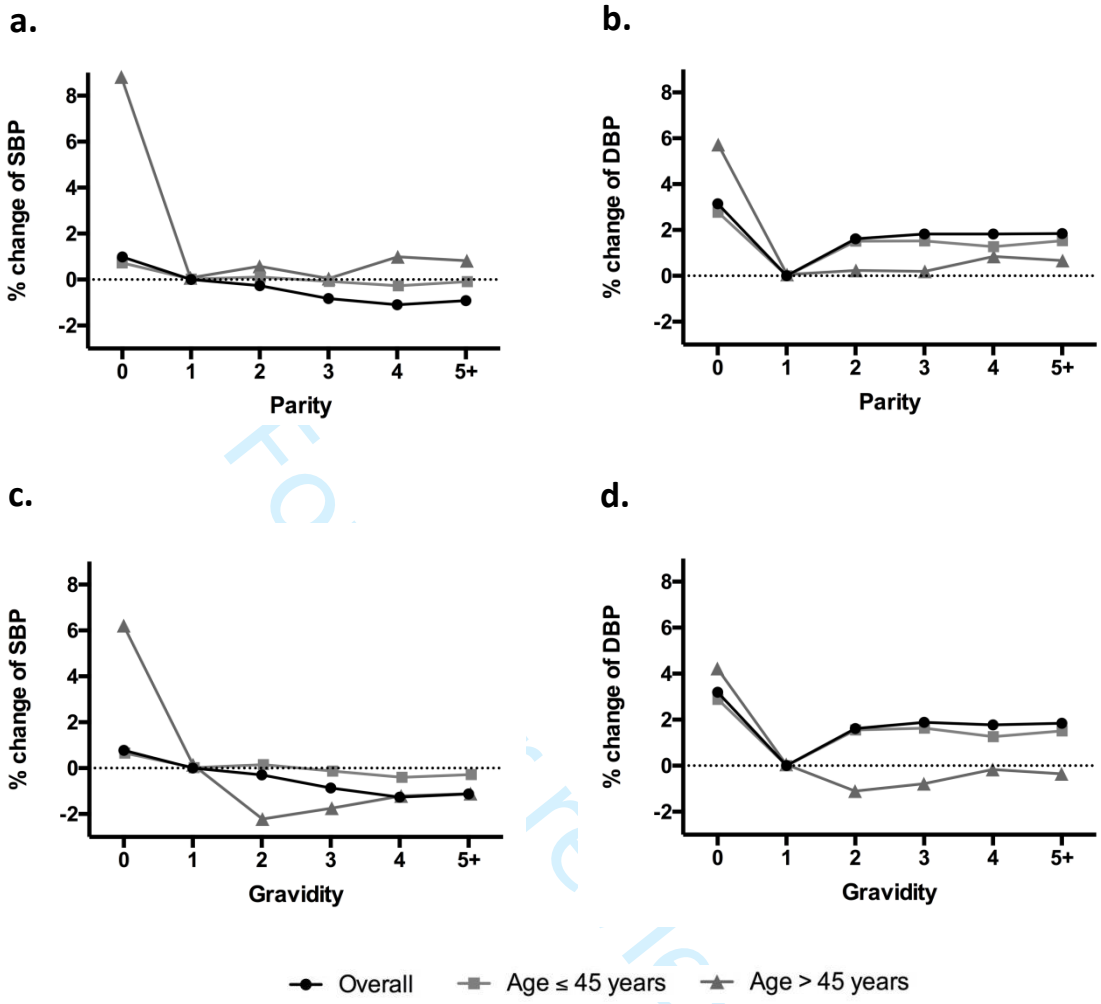
Figure 1. Adjusted % change for the association between reproductive history and blood pressure, overall, and stratified on 45-years of age: a) parity and systolic blood pressure (SBP); b) parity and diastolic blood pressure (DBP)



Supplemental Table 1. Adjusted hazard ratio (95% CI) for the association of gravidity and parity with mortality among 4013 women aged > 45 years in Bangladesh

	All-cause mortality	
	Model 1[1]	Model 2[2]
Parity		
0	4.00 (0.78, 20.59)	3.83 (0.74, 19.78)
1	Ref	Ref
2+	0.87 (0.57, 1.32)	1.90 (0.47, 7.65)
Gravidity		
0	3.58 (0.69, 18.43)	3.37 (0.65, 17.40)
1	Ref	Ref
2+	1.56 (0.39, 6.26)	1.57 (0.39, 6.34)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)
[1] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), BMI (kg/m^2), and number of abortions

Supplemental table 2. Adjusted % changes (95% CI) for systolic and diastolic blood pressure according to parity, restricting to 11 662 women with information on hormonal contraceptive (HC) use

	Systolic blood pressure		Diastolic blood pressure	
	Adjusted[1]	Adjusted + HC	Adjusted[1]	Adjusted + HC
Parity				
0	2.35 (0.58, 4.15)	2.82 (1.04, 4.63)	3.90 (2.08, 5.76)	4.34 (2.50, 6.20)
1	Ref	Ref	Ref	Ref
2+	0.02 (-0.87, 0.92)	-0.35 (-1.24, 0.54)	2.46 (1.53, 3.39)	2.11 (1.19, 3.04)
Gravidity				
0	2.15 (0.33, 4.00)	2.61 (0.78, 4.47)	3.74 (1.86, 5.64)	4.15 (2.27, 6.07)
1	Ref	Ref	Ref	Ref
2+	-0.04 (-0.97, 0.89)	-0.41 (-1.34, 0.52)	2.53 (1.57, 3.51)	2.19 (1.22, 3.16)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Supplemental table 3. Adjusted % changes (95% CI) for systolic and diastolic blood pressure according to parity, restricting to 21 111 women without taking an antihypertensive medication

	Systolic blood pressure			Diastolic blood pressure		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Parity						
0	2.47 (1.27, 3.69)	1.34 (0.18, 2.52)	0.99 (-0.13, 2.13)	4.37 (3.09, 5.67)	3.48 (2.23, 4.75)	3.02 (1.83, 4.22)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	3.48 (2.92, 4.04)	-0.29 (-0.85, 0.28)	-0.34 (-0.89, 0.22)	4.89 (4.30, 5.48)	1.93 (1.32, 2.54)	1.84 (1.25, 2.44)
Gravidity						
0	2.50 (1.25, 3.76)	1.23 (0.03, 2.45)	0.91 (-0.26, 2.09)	4.55 (3.23, 5.90)	3.55 (2.25, 4.87)	3.12 (1.88, 4.37)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	3.46 (2.88, 4.05)	-0.33 (-0.92, 0.26)	-0.40 (-0.98, 0.18)	5.00 (4.38, 5.62)	2.00 (1.36, 2.64)	1.88 (1.26, 2.50)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II)
[2] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)
[3] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Supplemental Table 4. Crude and adjusted odds ratios (95% CI) of having hypertension[4] according to parity and gravidity

	Parity			Gravidity		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.66 (1.99, 3.56)	1.96 (1.46, 2.65)	1.87 (1.38, 2.54)	2.49 (1.84, 3.38)	1.78 (1.30, 2.43)	1.70 (1.23, 2.33)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	3.14 (2.64, 3.73)	1.36 (1.13, 1.63)	1.34 (1.11, 1.62)	3.05 (2.55, 3.66)	1.30 (1.07, 1.57)	1.27 (1.05, 1.55)
Age ≤ 45 (n = 17621)						
0	2.18 (1.57, 3.01)	1.72 (1.23, 2.39)	1.64 (1.17, 2.29)	2.14 (1.52, 3.00)	1.64 (1.15, 2.32)	1.56 (1.10, 2.22)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.32 (1.93, 2.79)	1.24 (1.02, 1.51)	1.28 (1.05, 1.57)	2.34 (1.92, 2.84)	1.23 (1.00, 1.51)	1.28 (1.04, 1.58)
Age > 45 (n = 4013)						
0	3.46 (1.52, 7.89)	3.48 (1.52, 7.94)	3.96 (1.68, 9.35)	1.96 (0.85, 4.52)	1.98 (0.86, 4.56)	2.29 (0.96, 5.46)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	1.67 (0.93, 3.02)	1.67 (0.92, 3.01)	1.67 (0.92, 3.07)	1.10 (0.62, 1.96)	1.10 (0.61, 1.96)	1.05 (0.57, 1.91)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II)

[2] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)

[3] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

[4] Hypertension defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg based on the 2017 American College of Cardiology and American Heart Association (ACC/AHA) Guideline

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups. (Not applicable to this study)

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Gravidity, parity, blood pressure, and mortality among women in Bangladesh from the HEALS cohort

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Abstract

Objectives: Despite a hypothesized connection of reproductive history with hypertension and mortality, the nature of this association is poorly characterized. We evaluated the association of parity and gravidity with blood pressure, hypertension, and all-cause mortality.

Design: Prospective cohort study.

Setting: Health Effects of Arsenic Longitudinal Study (HEALS) cohort in rural Bangladesh

Participants: There were 21 634 Bangladeshi women recruited in 2000-2002, 2006-2008, and 2010-2014 included in the present analysis.

Methods: Reproductive history was ascertained through an interviewer-administered questionnaire at the baseline visit. Blood pressure was measured by a trained study physician following a standard protocol at the baseline visit. Vital status was ascertained at the biennial follow-up of study participants through June 2017. Linear and logistic regression models estimated the relationship between parity and gravidity with blood pressure and hypertension, respectively. Cox proportional hazards models estimated the relationship with all-cause mortality only among women aged > 45 years.

Results: Diastolic blood pressure was lowest in women with parity one (reference) and elevated in nulliparous women (adjusted % change = 3.12; 95% CI: 1.93, 4.33) and women with parity ≥ 2 (adjusted % change = 1.71; 95% CI: 1.12, 2.31). The associations with nulliparity were stronger for women aged > 45 years. Similar association patterns were observed with hypertension. Further, in nulliparous women aged > 45 years, 265 deaths (6.6%) were ascertained during the follow-up period (median follow-up time = 8 years), and we observed suggestive elevated risks of all-cause mortality (adjusted HR = 3.83; 95% CI: 0.74, 19.78). The

relationships between reproductive history, blood pressure, hypertension, and mortality were similar when modeling reproductive history as gravidity rather than parity.

Conclusions: For women in rural Bangladesh, nulliparity and nulligravidity appear to be associated with higher blood pressure and subsequent elevated risk of mortality

Keywords: Public health, epidemiology, hypertension

Strength and limitations of this study

- Large, rigorously conducted prospective study in a middle-income country context.
- Childbearing history was self-reported, and menopause status was not ascertained.
- Unmeasured confounders may remain unaccounted for in our analyses.

INTRODUCTION

Elevated blood pressure is an established risk factor for cardiovascular diseases (CVDs) (1, 2), and complications of hypertension account for approximately 9.4 million deaths worldwide (3). In Bangladesh, as in other South Asian countries, hypertension is a significant health concern with an overall prevalence of 26.4% among adults, with a higher prevalence (32.4%) in women (4).

A woman's risk for developing hypertension is influenced by several factors, including age, body mass index (BMI), menopause, dietary behavior, and physical activity (4, 5). Previous research has also provided suggestive evidence that pregnancy and childbirth influence blood pressure and subsequent morbidity and mortality. Pregnancy and childbirth may affect long-term cardiovascular health by several mechanisms, some of which are thought to be protective (elevated estrogen levels during pregnancy (6, 7)), and others of which are thought to increase risk (functional vascular property changes, decreased lipid and glucose metabolism, oxidative stress (8-11), and hemodynamic changes during pregnancy (12)). Further complicating the evaluation of this relationship is the possibility that a subset of nulliparous and nulligravid women did not conceive because of an underlying health issue, which may be an independent risk factor for CVD, such as polycystic ovary syndrome and uterine leiomyoma (13, 14).

Studies, largely in populations of European descent, have investigated the association between reproductive history and blood pressure (12, 15-21). Still, the findings have been equivocal and have not adequately addressed the effect of nulliparity and nulligravidity. Studies investigating parity and mortality have also been inconsistent, and these studies have differed in study design, sample size, or confounders for which a study adjusted (22-27). Two large meta-analyses of cohort studies (26, 27), largely without South Asian participants, suggest J-shaped

associations, with parities of one to six negatively related to all-cause and CVD mortality, and nulliparous women at increased risk. Only one study, using data collected from 1982 to 1998, has examined the effect of parity on all-cause mortality among Bangladeshi women aged 45 to 55 years and observed no association (28).

Given the multiple pathways that may connect reproductive history to morbidity and mortality, it remains unclear whether any associations found in other populations are also valid for the Bangladeshi context as well as other middle-income countries. Therefore, this study aimed to evaluate the associations of parity and gravidity with blood pressure and mortality in Bangladeshi women.

METHODS

Study population

The Health Effects of Arsenic Longitudinal Study (HEALS) is an ongoing population-based study in Araihazar, Bangladesh. To establish the cohort, a sampling frame was developed based on demographic, geographic, and well water arsenic data collected through a complete enumeration of the geographically defined 25-km^2 study area through a house-to-house survey, as has been detailed elsewhere (29). Between October 2000 and May 2002, we recruited 11 746 participants (5042 males and 6704 females) who met the following eligibility criteria: 1) married couples/individuals (to reduce loss to follow-up); 2) aged 18 to 75 years; 3) users of a tube well as a primary water supply; and, 4) residents of the study area for at least 5 years. During 2006-2008 (ACE I) and 2010-2014 (ACE II), the cohort was expanded to include an additional 8287 (3121 males and 5166 females) and 15 018 participants (5039 males and 9979 females), respectively, using rosters established based on well water arsenic measurements in the same study area following the same recruitment methods. The overall response rate among those

approached for participation was 97.5%. Study participants underwent clinical assessment and face-to-face structured interviews to ascertain demographic and lifestyle characteristics. Enrolled participants were subsequently visited biennially for follow-up evaluation at their home, including face-to-face interviewer-administered interviews and clinical assessment. More detailed information, including study design and data collection, can be found elsewhere (29). The study protocol was approved by the institutional review boards of The University of Chicago, Columbia University, the University of Illinois at Chicago, and the Bangladesh Medical Research Council. Verbal consent, in the presence of a witness, was obtained from each eligible respondent who agreed to participate in the study; verbal consent was obtained to facilitate participation among individuals with low literacy. In the present study, we restricted our analyses to the 21 634 women (99%) with no missing data on exposures, outcomes, and covariates of interest.

Assessing parity and gravidity

The primary exposure variables are the number of total births (parity) and the number of pregnancies (gravidity). Gravidity, number of livebirths, number of stillbirths, and number of abortions were obtained from the interviewer-administered baseline questionnaire. Parity was derived by subtracting the number of abortions from the total number of pregnancies.

Assessing blood pressure

Blood pressure was measured by a trained study physician using an automated sphygmomanometer with a digital display at the baseline visit (30). Subjects remained seated for 5 min, and blood pressures were taken with the cuff around their upper left arms. After 5 minutes of rest, a second reading was taken and averaged with the first. Participants were asked by trained interviewers to list any medications they were currently taking, and 2.4% (n = 523)

reported taking antihypertensive medication. For those participants, 10 and 5 mmHg were added to their observed systolic and diastolic blood pressures, respectively, to account for the magnitude of the potential treatment effect (31, 32). In subsequent analyses, blood pressure was modeled as a natural log-transformed continuous variable to improve normality. Hypertension was also defined based on the Joint National Committee (JNC) 8 Guideline as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg (33).

Assessing mortality

The vital status of each participant was ascertained at biennial follow-up visits through June 2017. Follow-up time was calculated as the number of days between the baseline visit and date of death or, if alive, the date of the last report of being alive.

A verbal autopsy (VA) procedure, previously validated by the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B), was implemented to investigate and assign the cause of death for the study participants in the HEALS cohort. In brief, an in-person interview with the informant (relatives or neighbors) of the deceased participant was conducted by a trained study physician to complete the VA questionnaire. If the death occurred in the hospital, supplemental documents regarding disease condition prior to death from the hospital, treating physician, or death certificate were obtained. A panel of expert physicians assigned a single cause of death. We coded the assigned cause of death based on the World Health Organization's (WHO) tenth revision of the International Classification of Disease (ICD-10) (34). Deaths classified with ICD-10 codes I00-I99 were attributed to CVD.

Assessing covariates

Self-reported participant characteristics including age, years of education, occupation (daily laborer/farmer, factory worker, business, homemaker, other), smoking status (current, former,

never), and land ownership (yes, no) were derived from the baseline interviewer-administered questionnaire. BMI was calculated as measured weight in kilograms divided by measured height in meters squared; a trained study physician measured both during the baseline interview following a standard protocol.

Statistical analysis

We assessed associations between participant characteristics and parity using analysis of variance for continuous variables and Pearson chi-squared tests for dichotomous variables. Since qualitative examination of the data (**Figure 1**) revealed no variation in the observed effects for parity and gravidity of two, three, four, or more, parity and gravidity were subsequently analyzed as three category variables: 0, 1, and ≥ 2.

Blood pressure and hypertension

Linear regression models were used to estimate the % changes and 95% confidence intervals (CIs) in both systolic and diastolic blood pressures. The % change was calculated as $(e^{\beta} - 1) \times 100\%$, with 95% CIs calculated as $(e^{(\beta \pm 1.96 \times SE)} - 1) \times 100\%$. Logistic regression models were used to estimate odds ratios (ORs) and their CIs for the associations of the dichotomous hypertension variable with parity and gravidity. Three models were fit: 1) adjusted for cohort (HEALS, ACE I, ACE II); 2) adjusted for cohort and age (years); and, 3) adjusted for cohort, age, years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (current, former, never), and BMI (kg/m^2). Since menopause is an important risk factor for elevated blood pressure (35, 36), the blood pressure analyses were repeated separately for women aged ≤ 45 years (n = 17621) and women aged > 45 years (n = 4013) since menopause status was not available. Arsenic was not included in the analyses since no confounding effect was observed.

Mortality

Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% CIs for the association of parity and gravidity with all-cause mortality and CVD mortality among 4 013 women aged > 45 years. Two models were fit: 1) adjusted for cohort and age; and 2) further adjusted including cohort, age, years of education, formal education, land ownership, smoking status, and BMI (kg/m^2), and number of abortions.

Sensitivity analyses

Two sensitivity analyses were conducted to test the robustness of the analyses. The first sensitivity analysis restricted to 11 662 women (54%) from the first two recruitment cycles with available information on hormonal contraceptive use since hormonal contraceptive use may also confound the relationship between reproductive history and cardiovascular health (37). Of 11 662 women, 26% (n = 3 018) had used hormonal contraceptives. On this subset, the adjusted model was re-run for the blood pressure and hypertension outcomes, including current hormonal contraceptive use as an additional covariate. In the second sensitivity analysis, we defined hypertension based on the 2019 American College of Cardiology and American Heart Association (ACC/AHA) Guideline as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg (38).

Patient and public involvement

There was no patient or public involvement in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Table 1 shows the characteristics of all 21 634 women, overall and by parity. Since gravidity correlated with parity in the present study (r = 0.98), participant characteristics in relation to gravidity are not shown in **Table 1**. The average number of total births was 3.8 (SD = 2.4), with a range of 0 to 15 births and a mode of 2. A total of 605 (2.8%) women were nulliparous. The means of systolic and diastolic blood pressure were 114.4 and 75.0 mmHg, respectively, and the prevalence of hypertension was 5.7%. The mean age of the study participants was 34.9 years (range: 18-65 years). Almost all women in the study were never-smokers. In parous women, increased age, no formal education, tobacco use, and land ownership were associated with higher parity. Furthermore, parity was positively associated with systolic and diastolic blood pressures and the prevalence of hypertension.

Table 1. Selected characteristics of 21634 Bangladeshi women in the HEALS cohort

Characteristics	All (N = 21 634)	Total parity			P-value[1]
		0 (n = 605)	1 (n = 2731)	2+ (n = 18 298)	
Systolic BP (mmHg) (mean ± SD)[2]	114.37 (17.07)	113.61 (17.92)	109.83 (12.99)	115.07 (17.46)	<0.0001
Diastolic BP (mmHg) (mean ± SD)[2]	75.01 (10.90)	75.03 (11.01)	71.64 (10.06)	75.50 (10.92)	<0.0001
Hypertension [n (%)]	1239 (5.7)	30 (5.0)	52 (1.9)	1157 (6.3)	<0.0001
Age (year) (mean ± SD)	34.87 (10.67)	28.46 (9.69)	24.73 (6.39)	36.59 (10.28)	<0.0001
Formal education [n (%)]					<0.0001
Yes	12 697 (58.7)	429 (70.9)	2323 (85.1)	9945 (54.4)	
No	8937 (41.3)	176 (29.1)	408 (14.9)	8353 (45.7)	
Land ownership [n (%)]					0.02
Yes	10 167 (47.0)	293 (48.4)	1214 (44.5)	8660 (47.3)	
No	11 467 (53.0)	312 (51.2)	1517 (55.6)	9638 (52.7)	
Occupation [n (%)]					0.04
Daily laborer/farmer	46 (0.2)	1 (0.2)	3 (0.1)	42 (0.2)	
Factory worker	741 (3.4)	15 (2.5)	82 (3.0)	644 (3.5)	
Business	403 (1.9)	9 (1.5)	62 (2.3)	332 (1.8)	
Homemaker	19 845 (91.7)	553 (91.4)	2500 (91.5)	16 792 (91.8)	
Other	599 (2.7)	27 (4.4)	84 (3.0)	488 (2.7)	
Smoking status [n (%)]					<0.0001
Current	486 (2.3)	11 (1.8)	17 (0.6)	458 (2.5)	
Former	449 (2.1)	4 (0.7)	9 (0.3)	436 (2.4)	
Never	20 669 (95.7)	590 (97.5)	2705 (99.05)	17 404 (95.1)	
BMI (kg/m^2) (mean ± SD)[3]	20.70 (3.57)	21.14 (3.82)	20.85 (3.37)	20.66 (3.59)	0.0004
Number of abortions (mean ± SD)	0.18 (0.50)	0.08 (0.35)	0.15 (0.44)	0.19 (0.51)	<0.0001

[1] Analysis of variance for continuous variable and Pearson chi-squared test for dichotomous variables

[2] Blood pressure

[3] Body mass index

Association between blood pressure, hypertension, parity, and gravidity

Table 2 summarizes the associations of parity with blood pressure**.** Compared with women with a parity of one, nulliparous women and women with a parity ≥ 2 were more likely to have higher blood pressure in Model 1. The magnitude of the associations changed considerably after adjusting for age (Model 2), suggesting age is an important confounder. The associations were further attenuated when we additionally adjusted for other confounders (Model 3). Model 3 shows that, overall, women with a parity of one have the lowest blood pressure, and both nulliparous and parity ≥ 2 associate with higher diastolic blood pressure. The confidence intervals of the estimates for systolic blood pressure are consistent with the null, although the magnitude of the estimates suggests an increase in systolic pressure for nulliparous women. After stratifying at 45 years of age, the associations with nulliparity were attenuated for women aged ≤ 45 years, while larger effect sizes were seen for women aged > 45 years.

Table 2. Crude and adjusted % changes (95% CI) for systolic and diastolic blood pressure according to parity

Parity	Systolic blood pressure			Diastolic blood pressure		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.89 (1.64, 4.16)	1.42 (0.23, 2.62)	1.04 (-0.11, 2.20)	4.76 (3.46, 6.08)	3.62 (2.35, 4.90)	3.12 (1.93, 4.33)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	4.07 (3.49, 4.66)	-0.55 (-1.13, 0.04)	-0.57 (-1.14, -0.00)	5.34 (4.74, 5.94)	1.77 (1.15, 2.39)	1.71 (1.12, 2.31)
Age ≤ 45 (n = 17621)						
0	1.86 (0.68, 3.05)	1.06 (-0.09, 2.22)	0.72 (-0.39, 1.85)	4.18 (2.86, 5.52)	3.21 (1.91, 4.51)	2.78 (1.55, 4.03)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.41 (1.86, 2.95)	-0.24 (-0.83, 0.34)	0.00 (-0.56, 0.57)	4.38 (3.77, 4.99)	1.16 (0.52, 1.80)	1.49 (0.87, 2.11)
Age > 45 (n = 4013)						
0	8.34 (1.87, 15.22)	8.36 (1.92, 15.20)	8.69 (2.52, 15.24)	5.29 (-0.23, 11.11)	5.29 (-0.23, 11.11)	5.67 (0.50, 11.10)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	0.96 (-2.90, 4.97)	0.89 (-2.95, 4.87)	0.68 (-2.98, 4.49)	0.71 (-2.66, 4.20)	0.71 (-2.67, 4.20)	0.57 (-2.57, 3.82)

[1] Adjusted for cohort (HEALS, ACE I, ACE II)

[2] Adjusted for cohort (HEALS, ACE I, ACE II) and age (years)

[3] Adjusted for cohort (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Table 3 summarizes the associations of gravidity with blood pressure, which have similar patterns to those observed with parity. While no relationship between gravidity and systolic blood pressure was found, we observed positive associations of nulligravid and gravidity ≥ 2 with diastolic blood pressure. As with the parity analysis, we observed stronger relationships for women aged > 45 years, where nulligravidity was associated with higher systolic and diastolic pressures.

Table 3. Crude and adjusted % changes (95% CI) for systolic and diastolic blood pressure according to gravidity

Gravidity	Systolic blood pressure			Diastolic blood pressure		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.82 (1.52, 4.14)	1.22 (-0.02, 2.47)	0.86 (-0.33, 2.07)	4.88 (3.53, 6.25)	3.63 (2.32, 4.96)	3.17 (1.92, 4.43)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	4.03 (3.42, 4.65)	-0.61 (-1.22, -0.00)	-0.67 (-1.26, -0.07)	5.44 (4.81, 6.08)	1.83 (1.19, 2.48)	1.74 (1.12, 2.36)
Age ≤ 45 (n = 17 621)						
0	1.90 (0.68, 3.14)	1.01 (-0.19, 2.22)	0.68 (-0.48, 1.85)	4.40 (3.03, 5.79)	3.31 (1.97, 4.66)	2.89 (1.61, 4.18)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.43 (1.86, 3.00)	-0.24 (-0.83, 0.36)	-0.02 (-0.61, 0.57)	4.50 (3.86, 5.14)	1.25 (0.59, 1.92)	1.54 (0.90, 2.19)
Age > 45 (n = 4013)						
0	4.98 (-1.65, 12.07)	5.05 (-1.56, 12.09)	6.03 (-0.34, 12.81)	3.13 (-2.59, 9.18)	3.13 (-2.59, 9.18)	4.18 (-1.21, 9.87)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	-1.01 (-5.15, 3.31)	-1.09 (-5.21, 3.20)	-1.35 (-5.28, 2.73)	-0.22 (-3.88, 3.57)	-0.22 (-3.88, 3.57)	-0.44 (-3.84, 3.09)

[1] Adjusted for cohort (HEALS, ACE I, ACE II)
[2] Adjusted for cohort (HEALS, ACE I, ACE II) and age (years)
[3] Adjusted for cohort (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Table 4 presents the associations of parity and gravidity with hypertension. In model 3, nulliparous women had a higher risk of having hypertension compared with women with a parity of one. As with the analyses in relation to blood pressure, larger effect estimates were observed for women aged > 45 years, although the confidence intervals contained the null. No significant associations were observed in relation to gravidity.

Table 4. Crude and adjusted odds ratios (95% CI) of having hypertension according to parity and gravidity

	Parity			Gravidity		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.71 (1.71, 4.28)	1.80 (1.12, 2.87)	1.71 (1.06, 2.75)	2.36 (1.44, 3.86)	1.50 (0.91, 2.49)	1.44 (0.86, 2.39)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	3.54 (2.67, 4.69)	1.27 (0.95, 1.71)	1.25 (0.93, 1.69)	3.44 (2.56, 4.62)	1.21 (0.89, 1.65)	1.18 (0.85, 1.61)
Age ≤ 45 (n = 17621)						
0	1.99 (1.14, 3.47)	1.33 (0.75, 2.34)	1.28 (0.72, 2.27)	2.00 (1.10, 3.63)	1.28 (0.70, 2.34)	1.23 (0.67, 2.27)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.54 (1.86, 3.48)	1.02 (0.73, 1.42)	1.08 (0.77, 1.52)	2.69 (1.91, 3.78)	1.06 (0.73, 1.52)	1.12 (0.78, 1.62)
Age > 45 (n = 4013)						
0	2.48 (0.95, 6.49)	2.48 (0.95, 6.50)	2.67 (0.99, 7.21)	1.18 (0.44, 3.17)	1.18 (0.44, 3.18)	1.34 (0.48, 3.69)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	1.17 (0.58, 2.37)	1.17 (0.58, 2.37)	1.12 (0.54, 2.30)	0.74 (0.38, 1.44)	0.74 (0.38, 1.44)	0.69 (0.35, 1.36)

[1] Adjusted for cohort (HEALS, ACE I, ACE II)
[2] Adjusted for cohort (HEALS, ACE I, ACE II) and age (years)
[3] Adjusted for cohort (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)
[4] Hypertension defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg based on the Joint National Committee (JNC) 8 Guideline

Association between mortality, parity, and gravidity

We observed 265 deaths (6.6%) among 4 013 women aged > 45 years during the study period [median follow-up time = 8 years (range 5 days to 16.7 years)]. Of this, 101 women (38.1%) died of CVD-related causes, and no women died of childbirth-related conditions. Since the number of deaths was not sufficient to conduct analysis in relation to CVD mortality, **Supplemental Table 1** shows the associations of parity and gravidity with all-cause mortality. Although the confidence intervals were wide, and they included the null, elevated risks of all-cause mortality were observed for nulliparity and nulligravidity.

Sensitivity analyses

A sensitivity analysis was conducted to account for the potential confounding effect of hormonal contraceptive use restricted to the 11 662 women (54%) with available data. After additionally adjusting for contraceptive use, the associations of gravidity and parity with blood pressure became stronger, suggesting a negative confounding effect (**Supplemental Table 2**). A similar phenomenon was observed in relation to hypertension (data not shown). Additionally, we performed the analysis in relation to hypertension using the 2019 ACC/AHA Guideline to define hypertensive women. As shown in **Supplemental Table 3**, associations observed using this hypertension definition were stronger as compared to the original hypertension variable defined by the JNC 8 Guideline.

DISCUSSION

This analysis finds that in a population of women in rural Bangladesh, nulliparous women and women with a parity ≥ 2 have increased blood pressure, but only nulliparous women were observed to have a higher risk of hypertension. The associations with nulliparity were stronger in

women > 45 years old. Furthermore, there was suggestive evidence of higher subsequent mortality among nulliparous women aged > 45 years old. This study contributes valuable information to the current evidence on the impacts of reproductive history on the risk of CVD in a developing country context.

The proportion of women in our study who actively decided not to have children is unclear, but given the relatively high birth rate in Bangladesh, the proportion of women who are nulliparous or nulligravid due to underlying issues causing infertility may be larger than the proportion of such women in studies from countries with lower birth rates. This may explain why our results suggest a larger risk for nulliparous and nulligravid women than seen in some previous studies.

The associations between reproductive history, blood pressure, and hypertension found in our study are consistent with findings from three large studies based in the US, Korea, and Norway (12, 15, 21). However, all of these studies are in contrast to other studies conducted in US populations, which suggested no association (16) or a higher risk of hypertension with each additional birth (18, 19). The discrepancies may be due to modeling differences, as these studies compared grand parity (≥ 5 births) to low-to-moderate parity without including nulliparous women in the analyses.

Our analysis of parity may help clarify previous contradictory results on mortality. Using data collected from 1982 to 1998, a study among Bangladeshi women aged 45 to 55 years observed no association between parity and all-cause mortality (28). Another study of 518 Amish women with a mean age of 63.1 years also reported no association between parity and mortality (25). In contrast, a suggestive elevated risk of mortality in nulliparous women was observed in our analyses. The discrepancy in findings may be due to differences in the study populations

across different periods in time. A recent analysis in US women found a small increase in all-cause mortality in nulliparous women (24). Two recent meta-analyses (26, 27) and a Japanese cohort study (22) showed that nulliparous women have the highest risk of mortality, which is consistent with our findings. These studies, however, also found higher risks of all-cause or CVD mortality for women with a large number of total births (6-7 births), suggesting a J-shaped relationship between mortality and parity. The authors concluded that this might largely arise from behavior-related factors associated with parenting or socioeconomic position (i.e., higher parous women are more likely to have lower socioeconomic status). This was not seen in our study, possibly reflecting a different relationship between socioeconomic status and parity in rural Bangladesh. In the present study, women with more than five births were much less likely to have a formal education but more likely to own land. In addition, a few studies included in these meta-analyses did not adjust for age, and this might explain the inconsistency between previous research and our findings. The large difference in the magnitude of the associations observed in the present study suggests that the effect is likely to differ by study populations, sample sizes, and follow-up times.

A potential mechanism by which these effects occur is longer lifetime lactation duration. Lactation has been associated with short-term decreases in blood pressure as well as reduced risk of hypertension and cardiovascular disease in middle age due to potentially lowered stress reactivity from the prolonged release of oxytocin (39, 40). Further, accumulation of fat stores, insulin resistance, and increases in circulating lipid levels are reversed by the mobilization of those fat stores during lactation, with longer duration of lactation supporting more complete reversal of changes (41). In Bangladesh, the percentage of children breastfed in the second year of life is 92% (42), and thus higher parity would correlate with much longer lifetime lactation

duration in this population. While longer duration of breastfeeding may be explained by other maternal health behaviors in developed countries and therefore confound the relationship with cardiovascular health (39), this is likely not the case in Bangladesh where long duration of breastfeeding is the norm.

The present study has limitations that should be considered. First, since reproductive history was self-reported at the baseline visit, there is the possibility for misclassification of parity and gravidity, particularly among older women; however, we deem that self-reported parity is both reliable and valid (43). Additionally, menopausal status was not ascertained, and thus age was used as a proxy, which may have resulted in some misclassification. Even assuming some misclassification of menopausal status, the large changes in magnitude observed in the age-stratified analyses suggest that, on average, women over 45 years have a different relationship between reproductive history and hypertensive morbidity and mortality than younger women. Additionally, some unmeasured confounders, such as gestational weight gain (only a consideration for the findings related to parous women) (44, 45), underlying health issues (e.g., polycystic ovary syndrome and uterine leiomyoma), and other socioeconomic status-related variables (e.g., income), were not collected and remain unaccounted for in our statistical analyses. Lastly, understanding the effect of lactation on this relationship and independently could be explored to expand our understanding of maternal health benefits associated with lactation in developing countries.

In conclusion, we have investigated the effects of pregnancy and childbirth on blood pressure and mortality and found that nulliparous and nulligravid women have the highest risk of hypertension. We also observed a modest increase in diastolic blood pressure for parity and

gravidity higher than two. Future studies in populations with similar socioeconomic backgrounds and patterns of fertility are needed to confirm current findings.

Contributors: Maria Argos, Faruque Parvez, and Habibul Ahsan designed the study and directed its implementation, including quality assurance and control. Mohammed Shahriar, Alauddin Ahmed, and Tariqul Islam helped supervise the field activities. Yu-Hsuan Shih, Molly Scannell Bryan, and Maria Argos designed the study's analytic strategy. Yu-Hsuan Shih, Molly Scannell Bryan, Keriann Hunter Uesugi, and Maria Argos helped conduct the literature review and prepare the Methods and the Discussion sections of the text.

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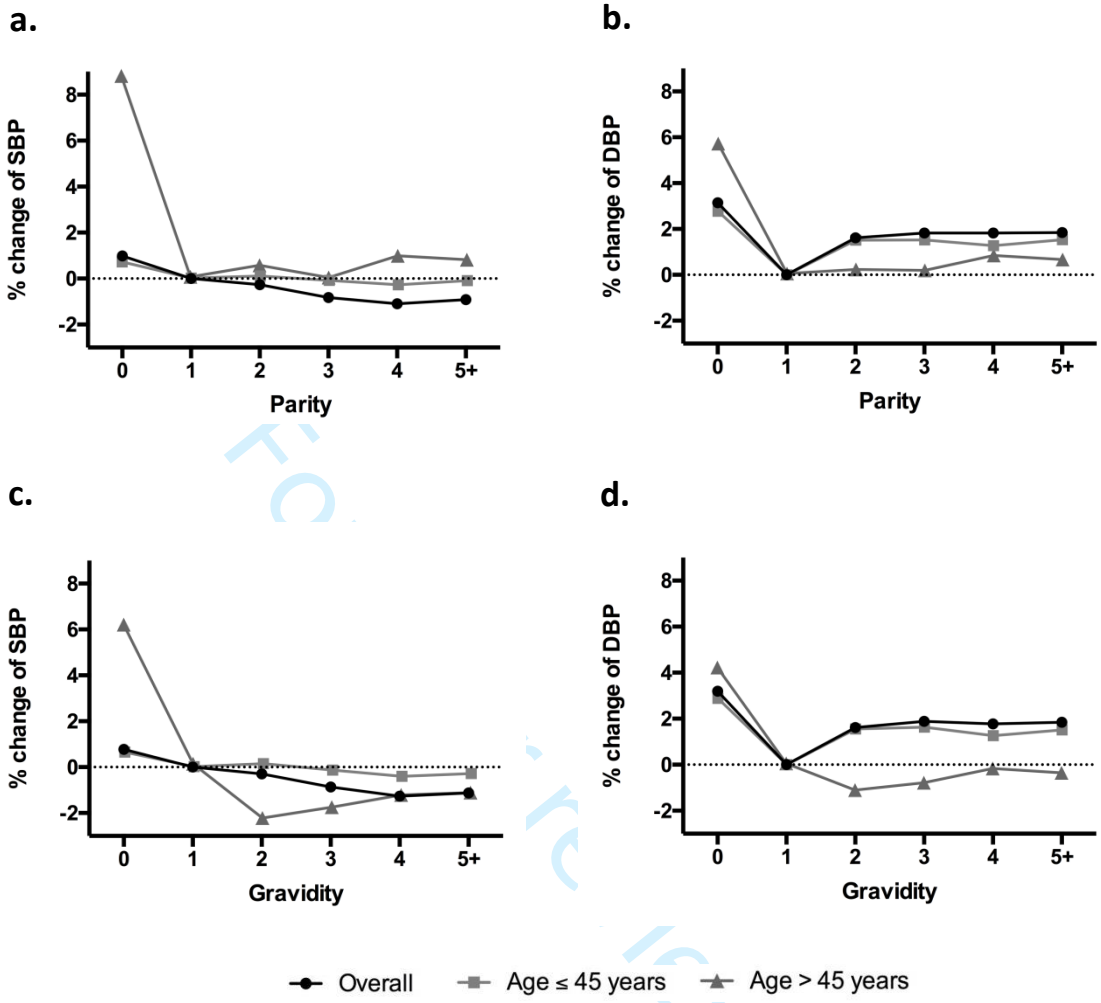
Figure 1. Adjusted % change for the association between reproductive history and blood pressure, overall, and stratified on 45-years of age: a) parity and systolic blood pressure (SBP); b) parity and diastolic blood pressure (DBP)



Supplemental Table 1. Adjusted hazard ratio (95% CI) for the association of gravidity and parity with mortality among 4013 women aged > 45 years in Bangladesh

	All-cause mortality	
	Model 1[1]	Model 2[2]
Parity		
0	4.00 (0.78, 20.59)	3.83 (0.74, 19.78)
1	Ref	Ref
2+	0.87 (0.57, 1.32)	1.90 (0.47, 7.65)
Gravidity		
0	3.58 (0.69, 18.43)	3.37 (0.65, 17.40)
1	Ref	Ref
2+	1.56 (0.39, 6.26)	1.57 (0.39, 6.34)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)
[1] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), BMI (kg/m^2), and number of abortions

Supplemental table 2. Adjusted % changes (95% CI) for systolic and diastolic blood pressure according to parity, restricting to 11 662 women with information on hormonal contraceptive (HC) use

	Systolic blood pressure		Diastolic blood pressure	
	Adjusted[1]	Adjusted + HC	Adjusted[1]	Adjusted + HC
Parity				
0	2.35 (0.58, 4.15)	2.82 (1.04, 4.63)	3.90 (2.08, 5.76)	4.34 (2.50, 6.20)
1	Ref	Ref	Ref	Ref
2+	0.02 (-0.87, 0.92)	-0.35 (-1.24, 0.54)	2.46 (1.53, 3.39)	2.11 (1.19, 3.04)
Gravidity				
0	2.15 (0.33, 4.00)	2.61 (0.78, 4.47)	3.74 (1.86, 5.64)	4.15 (2.27, 6.07)
1	Ref	Ref	Ref	Ref
2+	-0.04 (-0.97, 0.89)	-0.41 (-1.34, 0.52)	2.53 (1.57, 3.51)	2.19 (1.22, 3.16)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

Supplemental Table 3. Crude and adjusted odds ratios (95% CI) of having hypertension[4] according to parity and gravidity

	Parity			Gravidity		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Overall (n = 21 634)						
0	2.66 (1.99, 3.56)	1.96 (1.46, 2.65)	1.87 (1.38, 2.54)	2.49 (1.84, 3.38)	1.78 (1.30, 2.43)	1.70 (1.23, 2.33)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	3.14 (2.64, 3.73)	1.36 (1.13, 1.63)	1.34 (1.11, 1.62)	3.05 (2.55, 3.66)	1.30 (1.07, 1.57)	1.27 (1.05, 1.55)
Age ≤ 45 (n = 17621)						
0	2.18 (1.57, 3.01)	1.72 (1.23, 2.39)	1.64 (1.17, 2.29)	2.14 (1.52, 3.00)	1.64 (1.15, 2.32)	1.56 (1.10, 2.22)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	2.32 (1.93, 2.79)	1.24 (1.02, 1.51)	1.28 (1.05, 1.57)	2.34 (1.92, 2.84)	1.23 (1.00, 1.51)	1.28 (1.04, 1.58)
Age > 45 (n = 4013)						
0	3.46 (1.52, 7.89)	3.48 (1.52, 7.94)	3.96 (1.68, 9.35)	1.96 (0.85, 4.52)	1.98 (0.86, 4.56)	2.29 (0.96, 5.46)
1	Ref	Ref	Ref	Ref	Ref	Ref
2+	1.67 (0.93, 3.02)	1.67 (0.92, 3.01)	1.67 (0.92, 3.07)	1.10 (0.62, 1.96)	1.10 (0.61, 1.96)	1.05 (0.57, 1.91)

[1] Adjusted for cohort effect (HEALS, ACE I, ACE II)

[2] Adjusted for cohort effect (HEALS, ACE I, ACE II) and age (years)

[3] Adjusted for cohort effect (HEALS, ACE I, ACE II), age (years), years of education (years), formal education (yes, no), land ownership (yes, no), smoking status (yes, no), and BMI (kg/m^2)

[4] Hypertension defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg based on the 2017 American College of Cardiology and American Heart Association (ACC/AHA) Guideline

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7-9
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups. (Not applicable to this study)

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.